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(54) Title: IONTOPHORETIC TRANSDERMAL DELIVERY OF PEPTIDES

(57) Abstract: A method is disclosed for iontophoretically delivering a drug to a mammal, wherein the drug delivery profile may be adjusted by adjusting the concentration of electrolyte in the reservoir solution of the iontophoretic system.

IONTOPHORETIC TRANSDERMAL DELIVERY OF PEPTIDES

Field of the Invention

The subject invention relates to transdermal iontophoretic delivery of pharmaceutical compounds and compositions. More specifically, the subject invention relates to a method for controlling the delivery profile of pharmaceutical compounds and compositions.

Background of the Invention

Iontophoretic transdermal delivery of pharmaceutically active compounds (or "drugs") relates to introducing ions or soluble salts of the compounds into tissues of the body under the influence of an applied electric field. Recent reviews have summarized the features and benefits of iontophoretic transdermal delivery systems as compared with passive transdermal systems, as well as with other means of delivering pharmaceutical compounds into the bloodstream. Such reviews include, for example, O. Wong, *"Iontophoresis: Fundamentals," in Drugs Pharm. Sci. (1994), 62 (Drug Permeation Enhancement), 219-46 (1994);* and P. Singh et al., *"Iontophoresis in Drug Delivery: Basic Principles and Applications," Critical Reviews in Therapeutic Drug Carrier Systems, 11(2&3):161-213 (1994).* Thus, in certain cases when oral delivery or injection of a particular pharmaceutical compound may be ineffective or unacceptable because of poor gastrointestinal absorption, an extensive first pass effect, patient pain and discomfort, or other side effects, iontophoretic transdermal delivery may provide an advantageous method of delivering that compound.

Despite these advantages, iontophoretic methods appear limited as the drug delivery profile of a particular method depends heavily on the particular drug administered. Generally, once it has been established that a specific drug may be effectively delivered by iontophoresis, researchers have not enjoyed great success in

adjusting the delivery profile of that drug. Although researchers have experimented with the iontophoretic delivery of various drugs, specific information allowing one to tailor the delivery profile of a specific drug has not been available.

For example, European Patent Application No. 0 643 981 relates to the iontophoretic delivery of physiologically active peptides. The '981 patent briefly mentions the incorporation of dielectricity-conferring electrolytes into the iontophoretic method "as appropriate."

Boericke, et al., *Iontophoretic Delivery of Human Parathyroid Hormone (1-34) in Swine*, Proceed. Intern. Symp. Control. Rel. Mater. (1996) relates to the administration of PTH (1-34), but does not disclose the use of an electrolyte and does not disclose any method used to alter the delivery profile of the hormone.

Thus, a need exists for an iontophoretic delivery method that allows variable rate delivery of a specific drug tailored to a specific treatment.

Summary of the Invention

An object of the subject invention is to provide iontophoretic transdermal technology that provides the delivery of peptides through the human skin.

Still more specifically, an object of the subject invention is to provide a method for the delivery of a peptide, wherein the method includes applying a transdermal patch to the skin of a living body, wherein the transdermal patch has a reservoir comprising the peptide and about 0.005 to about 8 mmoles of a pharmaceutically acceptable electrolyte; and causing current to flow through the skin so as to iontophoretically deliver the peptide.

Another object of the invention is to provide an iontophoretic system for the delivery of a peptide through skin, wherein the system includes a transdermal delivery device attachable to the skin with the skin, the device including a first electrode and a second electrode, and a reservoir for containing a pharmaceutically acceptable electrolyte and the peptide in electrical communication with the first and second electrodes; and an electrical power source connected to the first and second electrodes; wherein the reservoir contains the peptide and about 0.005 to about 8 mmoles of the pharmaceutically acceptable electrolyte.

Brief Description of the Figures

Figure 1 plots the drug delivery profile of PTH (1-34) in minipigs as plasma concentration versus time.

Figure 2 plots the drug delivery profile of PTH (1-34) in minipigs as plasma concentration versus time.

Figure 3 plots the drug delivery profile of PTS 893 in minipigs as plasma concentration versus time.

Figure 4 plots the drug delivery profile of PTS 893 in minipigs as plasma concentration versus time.

Figure 5 plots the drug delivery profile of a subcutaneous injection of 20 μg of PTS 893 as plasma concentration versus time.

Detailed Description of the Preferred Embodiments

We have found that the delivery (dose and profile) by which a particular drug is administered to a patient may be controlled by suitable combination of the initial concentration of the drug and electrolyte and applied current (constant/variable) in the iontophoretic system. More specifically, we found that the combination of current density (constant/variable) and the initial amount of electrolyte allows the drug delivery profile to be adjusted. Even more specifically, we have found that setting the initial amount of the electrolyte in the iontophoretic system allows the drug delivery profile to be adjusted, particularly for peptides such as parathyroid hormones. For example, adjustments to the electrolyte concentration and current profile in an iontophoretic patch result in a drug delivery profile that more closely resembles the drug delivery profile provided by subcutaneous injection of the same drug. The ability to tailor the drug delivery profile in

iontophoresis therefore provides increased control of the drug's effects on the user, whether those effects are desired or undesired. Additionally, the ability to tailor drug delivery profile in iontophoresis may cause the iontophoretic delivery of drugs to be a more practically effective mode of administration.

As used herein, the term "drug delivery profile" means a plot of plasma concentration of the drug versus time for a given drug delivery period.

The electrolyte used in our method may include univalent or divalent ions. Examples of electrolytes used in our method include, but are not limited to, NaCl, $CaCl_2$, or $MgCl_2$. A preferred electrolyte is NaCl. The electrolyte may be present in amounts ranging from about 0.005 to about 8 mmole, preferably about 0.05 to about 1.0 mmole, more preferably about 0.05 to about 0.2 mmole. The initial amount of electrolyte may be expressed as a concentrations ranging from about 0.005 to about 2 M, preferably about 0.01 to about 0.2 M, more preferably about 0.05 to about 0.2 M.

While not wishing to be bound by any particular theory, it appears that when current is applied during the iontophoretic process, relatively smaller electrolyte ions carry the majority of the applied current while the drug carries a smaller percentage of the current. The electrolyte ion having the same positive or negative charge as the administered drug therefore competes for the current and carries a major fraction of current across the skin. Thus, an iontophoretic system utilizing a relatively low amount of starting electrolyte leads to reduced electrolyte concentration in the system or causes co-ion depletion to occur during the iontophoresis procedure. In this scenario, the peak drug delivery in the drug delivery profile occurs at a later time.

Conversely, (again, not wishing to be bound by any particular theory) when employing an excess electrolyte concentration in the iontophoretic system, little or no depletion of the electrolyte ions occurs. An excess electrolyte concentration should therefore permit a drug delivery profile that attains steady state conditions relatively early.

Typical drugs that may be administered by the method described herein include, but are not limited to, peptides such as calcitonin, insulin, and peptides and proteins having molecular weights of 10,000 or lower. Preferred peptides are oligo-peptides such as parathyroid hormones, or pharmaceutically acceptable salts thereof. As used herein, the

term "parathyroid hormones" includes parathyroid hormones such as the gene provided in Mangin et al., (Proc. Natl. Acad. Sci., U.S.A.), 86(7) 2408-12 (1989), the entire contents of which are incorporated herein by reference and analogues thereof. The terms parathyroid hormone and parathyroid hormone analogue refer to peptides and polypeptides and/or proteins having parathyroid activity and having at least 75% identity over the region corresponding to Seq. ID No.: 1 (*infra*). In addition, this invention contemplates using isolated amino acid molecules having an amino acid sequence portion identical to a consecutive 20 amino acid sequence portion of Seq. ID No.:1.

A more preferred peptide is PTH(1-34), and its pharmaceutically acceptable salts. Structurally, PTH (1-34) is a single peptide chain comprised of 34 amino acids from the N-terminal sequence of human parathyroid hormone:

Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe (Seq. ID No. 1)

PTH(1-34) has a molecular weight of 4118 and a calculated isoelectric point (pI) of 8.9. PTH(1-34) carries a net positive charge in aqueous solution at physiological pH.

The hydrochloride salt and acetate salt of PTH (1-34) are freely soluble in water. The hydrochloride salt is preferred.

The parathyroid hormones may be administered in a method for the treatment or prophylaxis of osteoporosis and related bone disorders in a host in need thereof. The host may be mammals, particularly humans.

With regard to parathyroid hormones, our method in one embodiment provides a drug delivery profile that can be varied to resemble or mimic the drug delivery profile attained from the subcutaneous injection of the same hormones. Thus, our method provides an acceptable delivery profile without disadvantages associated with injections, such as patient inconvenience and pain, patient compliance, and risk of infection.

The iontophoretic drug delivery method described herein generally involves applying a voltage/current across two electrodes on the skin so as to cause current to flow between the electrodes, wherein a part of the current is carried by ionic species of the

drug. During the delivery period, the current may be caused to flow by applying a constant, pulsed, or alternating voltage/current.

The pulsed or alternating voltage may have a frequency from about 0.01 Hz to about 100 kHz using substantially any type of waveform shape, including sine, square, triangular, sawtooth, rectangular, etc. In addition, the pulsed or alternating voltage may be applied on a duty cycle less than 100%.

The iontophoretic systems used to practice the subject invention may include devices and/or components selected from a wide variety of commercially available devices or components and/or from a wide range of methods and materials such as taught, for example, by patents and publications relating to such iontophoretic systems. In particular, the iontophoretic transdermal system may comprise an iontophoretic device such as is available from Iomed of Salt Lake City, Utah (e.g. IOMED™ model PM700 phoresor II), or a device such as manufactured by Empi of St. Paul, Minnesota (e.g. Empi DUPEL™), or a device known as the LECTRO™ Patch, manufactured by General Medical Device Corp. of Los Angeles, California.

The electrodes may be comprised of reactive or non-reactive electrodes. Examples of reactive electrodes are those made from metal salts, such as silver chloride or materials described in U.S. Pat. 4,752,285, the entire contents of which are incorporated herein by reference. The silver chloride electrodes are available from Iomed. Alternative reactive electrodes can be made from a combination of ion-exchange resins, exemplified by electrodes available from Empi. Examples of non-reactive electrodes are those made from metals such as gold or platinum, or from carbon particles dispersed in polymeric matrices such as one used in the LECTRO™ Patch. Adhesives used to fix the iontophoretic patch to the skin may be comprised of pressure sensitive adhesives used in passive transdermal delivery systems, such those derived from silicone or acrylic polymers, or those derived from rubbers such as polyisobutylene. A combination of pressure sensitive and conductive adhesives can also be used, such as those described EPA 0 542 294, the entire contents of which are incorporated herein by reference.

The drug reservoir contains the drug and electrolyte in either an aqueous solution or a gel. The reservoir gel may be comprised of water soluble polymers or hydrogels,

such as polyvinyl alcohol, or crosslinked hydrogels described in U.S. Pat. 5,069,908, the entire contents of which are incorporated herein by reference.

In the drug reservoir, the concentration of the drug may typically range from 0.1 to about 30 mg/ml, preferably about 1 to about 10 mg/ml, and more preferably about 1 to about 3 mg/ml. Th pH of the solution in the drug reservoir will typically range from 3.0 to 9.0, preferably 3.0 to 8.0, and more preferably from 4.0 to 7.0.

Additionally, the drug reservoir of the iontophoretic system may include additives that are well known and conventional in the iontophoresis art. Such additives include, for example, permeation enhancers, antioxidants, and buffers. When administering PTH (1-34), the presence of EDTA in the drug reservoir appeared to minimize the formation of PTH (1-33) during the procedure.

The representative unit dosage that may typically be delivered during a single delivery period may vary in amount from about 0.01 μg to about 200 mg. A preferred unit dosage for parathyroid hormones is about 0.005 to about 0.2 mg, more preferably about 0.005 to about 0.1 mg. The unit dosage that is delivered may be determined on the basis of a wide range of factors, including the compound, condition, age, body weight, clearance, etc.

Often, the iontophoretic delivery method of pharmaceutical compounds comprises a drug delivery treatment protocol that includes periodically applying an iontophoretic transdermal patch at intervals that may be as frequent as twice daily or as infrequent as once a week or once a month. Typically, in what is herein referred to as a single treatment step, the patch is applied, the drug is iontophoretically delivered and the patch is then removed, with another patch being applied again, when the next treatment step is due to be carried out. Although the absolute quantity of the drug delivered may vary substantially, a unit dosage is herein defined to be that quantity of drug, however large or small, that is delivered during a single treatment step by a single patch application at an individual site.

The iontophoretic system may be comprised of still other methods and materials, such as described in WO 92 17239, EPA 0 547 482, and U.S. Patent No. 4,764,164, the entire contents of which are incorporated herein by reference. The iontophoretic drug

delivery comprises a direct/pulsed/alternating current flow of about 0.001 to about 4 mA/cm^2 during the delivery phase of the drug. A preferred range for the current flow may be from about 0.01 to about 2 mA/cm^2. A more preferred range for the current flow may be from about 0.1 to about 0.5 mA/cm^2.

Generally, the transport area of the patch ranges from about 1.0 to about 100 cm^2, preferably about 1 to about 50 cm^2, and more preferably about 1 to about 30 cm^2.

Time period for drug delivery may typically range from about 10 seconds to about 48 hours, wherein the drug delivery period may preferably be from about 1 minute to about 24 hours. When administering PTH (1-34), reduction in the drug delivery period may minimize the formation of PTH (1-33) in the system. Also, to reduce the formation of PTH (1-33), it may be advantageous to wash the skin with regular soap prior to application of the iontophoretic patch.

Example 1

A TransQ™ iontophoretic system supplied by Dermion was modified by depositing additional silver chloride on silver foil by to increase the negative electrode's charge capacity to 810 mA.min. Polyethylene oxide was used as donor reservoir matrix for conditions #1 and 2 and Sontara nonwoven was used for conditions #3-6. The fill volume was 1.5 ml for conditions 1-5 and 1 ml for condition #6, transport area was 7 cm^2. Current was generated by constant current source (supplied by Dermion) and was manually adjusted to obtain variable current in cond #4 with PTS 893.

Example 2

PTH (1-34) was iontophoretically administered to male miniature pigs of the Gottinger strain and 12.4 - 18.0 kg body weight. The iontophoretic device had a silver foil anode (charge capacity of 1000 mA.min) and a silver chloride plated silver plate cathode (charge capacity of 810 mA.min). The electrodes were applied on the dorsum of the animals 5 cm apart and the constant current generated by a Phoresor.

The conditions used for these studies are shown below in Table 1. Current was applied for the first 3 hours in each condition, except for condition 1, during which current

was applied for 4 hours. Blood samples were taken during the application of current, and also up to 2 hours after the current was shut off.

TABLE 1

Ionto. Condition	PTH(1-34) conc. (mg/ml)	Matrix; Area (cm2)	Initial pH	Current Density (mA/cm2)	NaCl conc. (M)
1	6.0	PEO; 7	~ 6.0	0.47	0.2
2	3.0	PEO; 7	~ 6.0	0.47	0.2
3	3.0	Sontara; 7	~ 4.0	0.47	0.2
3	3.0	Sontara; 7	~ 4.0	0.30	0.2
5	3.0	Sontara; 7	~ 4.0	0.30	0.1
6	3.0	Sontara; 7 2 layers; 1 ml fill vol.	~ 4.0	0.30	0.1

Figures 1 and 2 show the data observed using the above iontophoretic conditions, with the values expressed as mean ± sem (n=6). A comparison of Condition 4 shown in Figure 1 and Condition 5 shown in Figure 2 reveals that when the NaCl concentration in the reservoir solution was lowered from 0.2 to 0.1 M, the plasma peak was delayed and total delivery increased.

Example 3

The conditions used for the iontophoretic administration of PTS-893 to minipigs are shown below in Table 2. The iontophoretic patch used contained 3.0 mg/ml of PTS-893 in a Sontara matrix. Blood samples were taken during the application of current, and also up to 2 hours after the current was shut off. For comparative purposes, 20 μg of PTS 893 was also administered by subcutaneous injection to minipigs.

TABLE 2

Ionto. Condition	Drug Electrode NaCl conc. (M)	Current Density & Duration	t_{max} (hr)	C_{max} (ng/ml)	$T_{½}$ (hr)	AUC (ng-hr/ml)
1	0.1	0.3 mA/cm2 for 3 hr	3.0-3.5	6.3 ± 1.8	~1.5	18.7
2	0.1	0.3 mA/cm2 for 2 hr	2.2-2.5	5.9 ± 2.5	~0.8	11.6
3	0.05	0.3 mA/cm2 for 1 hr	1.5-2.0	3.2 ± 1.8	~1.0	7.5
4	0.05	0.5 mA/cm2 for 0.5 hr; 0.1 mA/cm2 for 0.5 hr	1.2-2.0	1.7 ± 0.5	~0.8	0.8
Subcutaneous injection of 20 µg PTS 893			1.0-1.5	0.5 ± 0.07	~0.8	0.7

Figures 3 and 4 show the data observed using the above iontophoretic conditions, and Figure 5 shows the data observed after subcutaneous injection. A comparison of Figure 4 and Figure 5 shows that iontophoretic delivery provided a drug delivery profile substantially similar to subcutaneous injection.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and figures be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

We claim:

1. An iontophoretic method for the delivery of a peptide, wherein the method comprises:
   (a) applying a transdermal patch to the skin of a living body, wherein the transdermal patch has a reservoir containing the peptide and 0.005 to about 8 mmoles of a pharmaceutically acceptable electrolyte;
   (b) causing current to flow through the skin so as to iontophoretically deliver the peptide.

2. The method according to claim 1, wherein a constant current is applied.

3. The method according to claim 1, wherein a variable current is applied.

4. The method according to claim 1, wherein the peptide is a parathyroid hormone.

5. The method according to claim 1, wherein the peptide is a parathyroid hormone selected from the group consisting of PTH(1-84), PTH (1-33), PTH (1-34), PTH (1-37), PTH(1-38), PTH(1-54), PTH(1-34)-amide, PTH(1-37)Lys3, and PTS 893.

6. The method according to claim 1 wherein the current flow is at a level from about 0.01 to about 4 mA/cm.

7. The method according to claim 1, wherein the peptide concentration in the solution is about 0.1 to about 30 mg/ml.

8. The method according to claim 1, wherein the pH of the solution is about 4.0 to about 7.0.

9. The method according to claim 1 wherein a unit dosage of about 1 ng to about 100 mg of the peptide is delivered through the skin during the delivery step.

10. The method according to claim 3 wherein the unit dosage is delivered over a time period of about 0.25 to about 3 hours.

11. The method according to claim 1, wherein the peptide is a parathyroid hormone administered to a mammal for the treatment or prophylaxis of osteoporosis.

12. The method according to claim 1, wherein the peptide is a parathyroid hormone administered to a human for the treatment or prophylaxis of osteoporosis.

13. An iontophoretic system for the delivery of a peptide through skin, comprising

(a) a transdermal delivery device attachable to the skin, the device including a first electrode and a second electrode, and a reservoir for containing a pharmaceutically acceptable electrolyte and the peptide in electrical communication with the first and second electrodes;

(b) a electrical power source connected to the first and second electrodes;

wherein the reservoir contains the peptide and about 0.005 to about 8 mmoles of the pharmaceutically acceptable electrolyte.

14. The iontophoretic system of claim 13, wherein the peptide is a parathyroid hormone.

15. The iontophoretic system of claim 13, wherein the peptide is a parathyroid hormone selected from the group consisting of PTH(1-84), PTH (1-33), PTH (1-34), PTH (1-37), PTH(1-38), PTH(1-54), PTH(1-34)-amide, PTH(1-37)Lys3, and PTS 893.

16. The iontophoretic system of claim 13, wherein reservoir contains the pharmaceutically acceptable electrolyte and peptide in a solution having a pH ranging from about 4.0 to about 7.0.

17. The iontophoretic system of claim 13, wherein the peptide is present in the reservoir in a solution at a concentration of about 0.1 to about 30 mg/ml.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5 961 482 A (CHIEN ET AL.) 5 October 1999 (1999-10-05) column 2, line 23 -column 3, line 63 column 23 -column 24; example 19	1-3,6-9, 13,16 4,5,11, 12,15
Y	EP 0 643 981 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 22 March 1995 (1995-03-22) cited in the application page 11; examples 1-3 page 6, line 2 - line 4	4,5,11, 12,15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2001	25/06/2001

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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